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(54) Title: NON-HALOGENATED PHENYL SUBSTITUTED PHENOLS, ANTIMICROBIAL COMPOSITIONS CONTAINING THE SAME, AND METHODS OF USING THE SAME

(57) Abstract: An antimicrobial compound of formulas (Ia), (Ib) or (Ic), compositions containing the same, and method of using the same for reducing the presence of microorganism on a substrate or in a fluid environment comprising an antimicrobial effective carrier and at least one antimicrobial compounds including non-halogenated phenyl substituted phenol compounds; wherein R_1 and R_2 are each independently selected from the group consisting of hydrogen, an alkyl group optionally substituted with a cycloalkyl group, a hydroxyl group, or an aryl group; an alkenyl group; an alkoxy group; a cycloalkenyl group; an aryl group; benzyl optionally substituted with an alkyl group; and a cycloalkyl group wherein any one of which said groups can optionally be substituted with a hydroxyl; and R_3 is selected from the group consisting of hydrogen, an alkyl group optionally substituted with a hydroxyl, an aryl group, a benzyl, a benzyloxyl group, an alkoxy group, and a cycloalkyl group optionally substituted with hydroxyl; R_4 is selected from the group consisting of hydrogen and an alkyl group optionally substituted with a hydroxyl.

NON-HALOGENATED PHENYL SUBSTITUTED PHENOLS, ANTIMICROBIAL COMPOSITIONS CONTAINING THE SAME, AND METHODS OF USING THE SAME

Field of the Invention;

The present invention relates to antimicrobial compounds and compositions containing such compounds, and more particularly to phenyl substituted phenol compounds exhibiting antimicrobial activity, antimicrobial compositions containing phenyl substituted phenol compounds, and methods of using such compositions.

Background of the Invention;

Recently, attention has focused on personal hygiene in light of mounting concerns about public health. There is a growing awareness of various microorganisms and microbial pathogens such as yeast, fungi, bacteria, molds and viruses, that can cause disease upon access and entry into the body such as through the eyes, ears, nose, mouth and skin. These microbes are generally transmitted from a source (e.g. a contaminated surface) by the hands to a person's body. Thus, a number of illnesses may easily be prevented by decontamination of the skin and the hands. In a related vein, the control of pathogenic or otherwise undesirable microbes is also a concern in promoting good oral hygiene, where reducing populations of microorganisms on the teeth, gums and tongue has been shown useful in controlling dental plaque accumulation, gingivitis, oral malodor, and other oral maladies.

It has been shown that at least 18 percent of the population is afflicted with some form of a microbial infection of the dermis. Although such infections are more common in third world areas, there is also a substantial incidence of the infections in developed areas where a high level of personal hygiene exists. Studies have further shown that the factors that contribute to rising incidence of such infections include longer lifespans, emerging resistance of microbes to antibiotics,

increased use of antineoplastic agents, and a growing population of patients with some deterioration in their immune system.

Microbial infections and disease are caused by many types of microorganisms. Most infections are typically the result of microbial infection and/or the presence of microorganisms such as on the skin of the hand or foot, for example. Accordingly, it has been noted that effective treatments of such infections should also include proper preventive measures, specifically, thorough sanitization of the skin including the hands and contact surfaces to prevent further contamination and/or transmission to other individuals.

Treatment of infection typically includes the application of topical or systemic antibiotic/antifungal agents. Such therapies are disadvantageous because they exhibit a limited rate of success, are contraindicated and/or have undesirable drug interactions, produce elevated levels of toxicity, and/or are expensive. Additionally, the scientific and medical communities have moved away from the use of such systemic antimicrobial therapy for oral and general infection control due to an increase in the number of resistant strains of pathogenic microbes.

Antimicrobial cleansing compositions for use on the hands, skin, and scalp have used a variety of antimicrobial ingredients including anionic surface-active agent (e.g. sodium lauryl sulfate), coal tar, cationic antimicrobial agents such as chlorhexidine, and halogenated nonionic antimicrobial agents such as triclosan and hexachlorophene.

In addition to being present external to the body, microorganisms are also present in the oral cavity. Among undesirable microorganisms are Gram-positive and Gram-negative bacterial species associated with the formation of dental plaque (a dense, enamel-adherent biofilm consisting of microorganisms and their attendant extracellular matrix). Dental plaque is initially soft and removable by mechanical oral hygiene, but can undergo mineralization to form hard deposits of dental calculus. Although dental plaque may form on any part of the tooth surface, accumulation of plaque at the gingival margin is particularly implicated in the occurrence of gingivitis. Even with good oral hygiene, it has been shown that microorganisms rapidly multiply and build up in the oral

cavity, and many individuals have difficulty in maintaining good plaque control with brushing and flossing alone.

Specific areas, including periodontal and subgingival spaces, as well as interpapillary spaces of the tongue and tonsils provide a favorable environment for harboring bacteria and other microbes. Quite often the use of dentifrices such as toothpaste, and/or toothbrushes, dental flosses, and cosmetic mouthrinses, is insufficient to control the undesirable microorganisms. The persistence of these microorganisms in such environments greatly increases the risk of plaque and calculus build-up, which in turn presents a danger of gingival inflammation and more advanced forms of periodontal disease. In addition, the production of malodorous volatile compounds by accumulated populations of anaerobic microorganisms in dental plaque or on the tongue dorsum may lead to perceptible oral malodor.

Accordingly, it is highly desirable to include antimicrobial (antibacterial) agents in topical or oral compositions having biocidal and/or biostatic activity against a variety of microorganisms. Microorganisms of concern in hand and skin care include Gram-negative bacteria such as *Escherichia coli* and *Pseudomonas aeruginosa*, Gram-positive bacteria such as *Staphylococcus aureus* and *Propionibacterium acnes*, molds such as *Aspergillus niger* and *Penicillium funiculosum*, yeasts such as *Candida albicans, Saccharomyces cerevisiae* and *Pityrosporum ovale*, dermatophytic fungi such as *Trichophyton rubrum*, microalgae such as *Chlorella* spp. and *Spyrogyra* spp., and viruses such as Herpes virus and Picornavirus. Microorganisms of concern in dental plaque, gingivitis, malodor and other oral maladies in the oral cavity include *Fusobacterium nucleatum, Prevotella intermedia, Actinomyces viscosus, Streptococcus sanguis, Streptococcus mutans,* and *Candida albicans.*

One type of oral composition used as a standard in oral hygiene are mouthrinses. However, many of such mouthrinses have only been effective in masking halitosis. These include mouthrinses which comprise quaternary amines (e.g., combinations of ethanol and domiphen bromide and/or cetylpyridinium chloride) or mixtures of orally acceptable surface-active agents or surfactants.

Several mouthrinses that have been marketed for the reduction of plaque and gingivitis

generally rely on cationic agents such as chlorhexidine digluconate, antimicrobial essential oils (e.g., thymol, eucalyptol, ethanol, menthol and methyl salicylate) and/or water-insoluble phenolic agents such as triclosan.

The cationic antimicrobial materials such as chlorhexidine, benzethonium chloride, and cetyl pyridinium chloride have been investigated as antimicrobial agents for the control of gingivitis and/or oral malodor. The antimicrobial activity of these materials are theorized to be linked to the cationic charge of the amine group. This charge is attracted to negatively-charged moieties on the cell membrane or wall of the microorganism, and facilitates attachment to the surface of the microorganism. The attachment and subsequent interaction with the cell surface disrupts the cell membrane structure causing leakage of the intracellular fluids, eventually killing the microorganism. However, such materials are generally not effective when used with anionic materials and when other cationic minerals and organic molecules present in hard water which may interfere with attraction and subsequent attachment of the cationic materials to the negatively-charged moieties. These chemical interactions may thereby reduce the overall antimicrobial efficacy of this class of compounds. Noncationic antimicrobial materials, on the other hand can be compatible with anionic components of an oral antimicrobial composition or other type of compositions containing an antimicrobial agent.

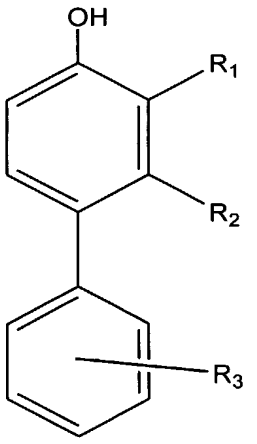
Halogenated hydroxydiphenyl ethers such as triclosan have been effectively employed in oral compositions as antimicrobial agents. However, halogenated compounds may present safety issues.

Alternatives to triclosan with similar antimicrobial activity have been the subject of continuing investigation. Alkyl substituted phenols, such as thymol (2-isopropyl-5-methyl phenol), are well known and widely used as antimicrobials. For example a fixed combination of thymol, menthol, eucalyptol, and methyl salicylate is used in commercial clinically effective anti-plaque/anti-gingivitis mouthrinse formulations. However, such essential oils may possess lower antimicrobial activity than triclosan. Non-halogenated alternatives to triclosan with similar or improved antimicrobial activity have been the subject of inventors' investigation.

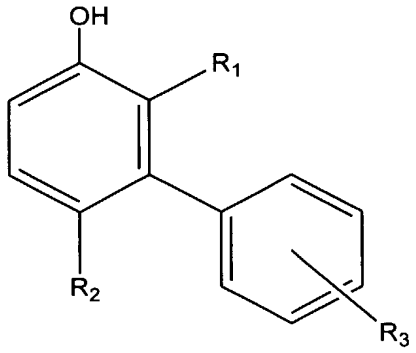
Accordingly, it would be a significant advance in the art of personal and dental hygiene to provide new antimicrobial compounds and compositions containing such compounds which exhibit substantial antimicrobial effectiveness and yet do not possess the safety concerns often associated with halogenated compounds such as triclosan.

Summary of the Invention;

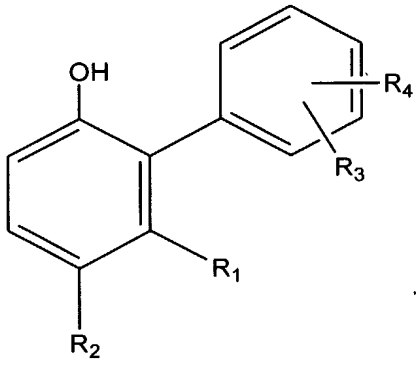
In accordance with the present invention, phenyl substituted phenol compounds exhibiting effective antimicrobial activity are disclosed. In one aspect of the invention, phenyl substituted phenol compounds are disclosed having the following formulas:



Ia



Ib



Ic

wherein

R_1 and R_2 are each independently selected from the group consisting of hydrogen, an alkyl group optionally substituted with a cycloalkyl group, a hydroxyl group, or an aryl group; an alkenyl

group; an alkoxy group; a cycloalkenyl group; an aryl group; benzyl optionally substituted with an alkyl group; and a cycloalkyl group wherein any one of which said groups may optionally be further substituted with hydroxyl; and

R_3 is selected from the group consisting of hydrogen, an alkyl group optionally substituted with a hydroxyl, an aryl group, a benzyl group, a benzyloxyl group, an alkoxy group, and a cycloalkyl group optionally substituted with hydroxyl;

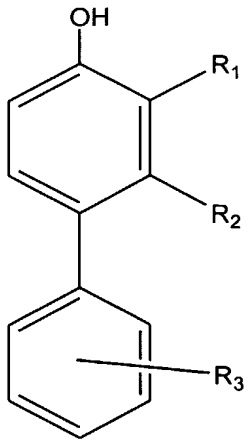
with the proviso that,

for compounds of Formula Ia, when R_1 is a C_{1-8} n-alkyl group or a C_{3-6} cycloalkyl group, each being optionally partially or fully substituted with a C_{3-6} cycloalkyl group or a C_{1-7} side chain alkyl group, and R_2 is hydrogen, then R_3 is not selected from the group consisting of a C_{1-8} n-alkyl group and a C_{3-6} cycloalkyl group, each being optionally partially or fully substituted with a C_{3-6} cycloalkyl group or a C_{1-7} side chain alkyl group;

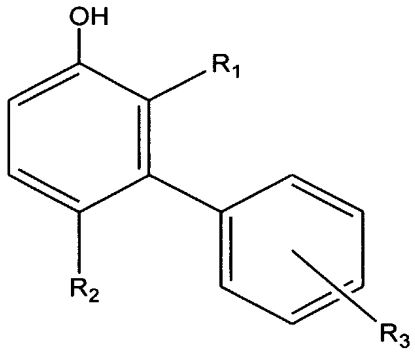
for compounds of Formulas Ia through Ic, when R_1 and R_2 are each hydrogen, then R_3 is not selected from the group consisting of a hydrogen, a 4-alkyl group, or a 2-benzyloxy group; and

for compounds of Formula Ic, wherein each of R_1, R_2, and R_4 is a hydrogen, then R_2 is not selected from the group consisting of a methyl group, ethyl group or a tert-butyl group.

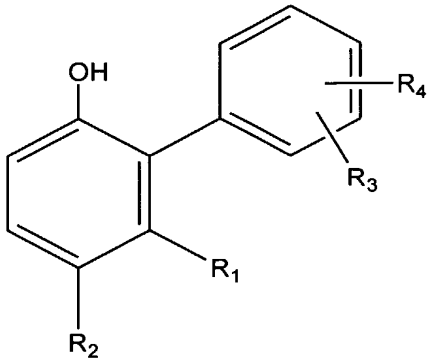
In another aspect of the present invention, an antimicrobial composition comprising an effective amount of at least one antimicrobial compound such as a phenyl substituted phenol compound for reducing the presence of microorganisms on a substrate or in a fluid environment in combination with an antimicrobial effective carrier. In such aspect of the invention, there is provided an antimicrobial composition comprising an antimicrobial acceptable carrier and an antimicrobial effective amount of at least one antimicrobial compound selected from the following formulas:



IIa



IIb



IIc

wherein

R_1 and R_2 are each independently selected from the group consisting of hydrogen, an alkyl group optionally substituted with a hydroxyl, a cycloalkyl group or an aryl group; an alkenyl group; an alkoxy group; a cycloalkenyl group; an aryl group; benzyl optionally substituted with an alkyl group; and a cycloalkyl group wherein any one of which said groups may optionally be substituted with a hydroxyl; and

R_3 is selected from the group consisting of a hydrogen, a hydroxyl, an alkyl group, benzyl, a benzyloxy group, an alkoxy group, and a cycloalkyl group optionally substituted with hydroxyl;

R_4 is selected from the group consisting of a hydrogen, and an alkyl group optionally substituted with a hydroxyl;

with the proviso that,

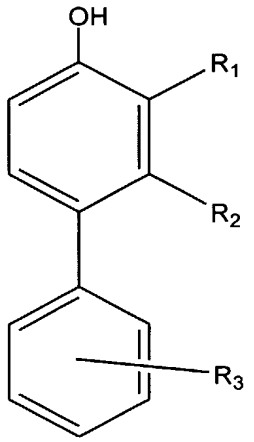
for compounds of Formula IIa, when R_1 is a C_{1-8} n-alkyl group or a C_{3-6} cycloalkyl group, each being optionally partially or fully substituted with a C_{3-6} cycloalkyl group or a C_{1-7} side chain alkyl group, and R_2 is hydrogen, then R_3 is not selected from the group consisting of a C_{1-8} n-alkyl

group and a C_{3-6} cycloalkyl group, each being optionally partially or fully substituted with a C_{3-6} cycloalkyl group or a C_{1-7} side chain alkyl group; and

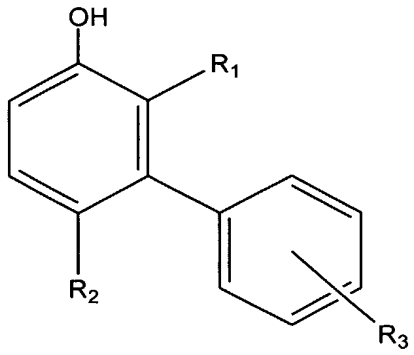
for compounds of Formulas IIa through IIc, when R_1, R_2, and R_4, are each hydrogen, then R_3 is not a hydrogen.

In another aspect of the invention there is provided an oral antimicrobial composition comprising an effective antimicrobial amount of at least one antimicrobial compound including phenyl substituted phenol compounds for reducing the presence of microorganisms in an oral cavity in combination with an orally acceptable carrier.

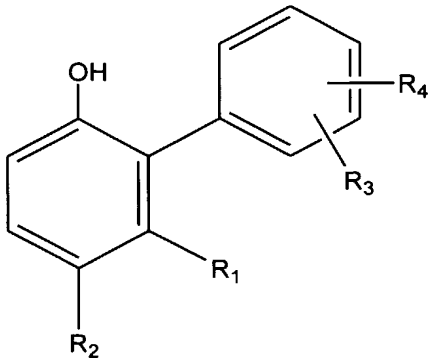
In this aspect of the present invention, an oral composition comprises an orally acceptable carrier and an antimicrobial effective amount of at least one antimicrobial compound selected from the following formulas:



IIIa



IIIb



IIIc

wherein

R_1 and R_2 are each independently selected from the group consisting of hydrogen, an alkyl group optionally substituted with a hydroxyl, a cycloalkyl group or an aryl group; an alkenyl group; an alkoxy group; a cycloalkenyl group; an aryl group; benzyl optionally substituted with an alkyl group; and a cycloalkyl group wherein any one of which said groups may optionally be substituted with a hydroxyl; and

R_3 is selected from the group consisting of a hydrogen, a hydroxyl, an alkyl group, a benzyl group, a benzyloxy group, an alkoxy group, and a cycloalkyl group optionally substituted with hydroxyl;

R_4 is selected from the group consisting of hydrogen, and an alkyl group optionally substituted with hydroxyl;

with the proviso that,

for compounds of Formula IIIa, when R_1 is a C_{1-8} n-alkyl group or a C_{3-6} cycloalkyl group, each being optionally partially or fully substituted with a C_{3-6} cycloalkyl group or a C_{1-7} side chain alkyl group, and R_2 is hydrogen, then R_3 is not selected from the group consisting of a C_{1-8} n-alkyl group and a C_{3-6} cycloalkyl group, each being optionally partially or fully substituted with a C_{3-6} cycloalkyl group or a C_{1-7} side chain alkyl group; and

for compounds of Formula IIIa, when R_1, R_2 and R_4 are each hydrogen, then R_3 is not hydrogen.

In a further aspect of the invention, methods are provided for using the antimicrobial composition comprising at least one antimicrobial compound selected from Formulas IIa-IIc for reducing the presence of microorganisms on a substrate. The methods include treating the substrate with an effective amount of the antimicrobial composition containing the antimicrobial compounds selected from Formulas IIa-IIc.

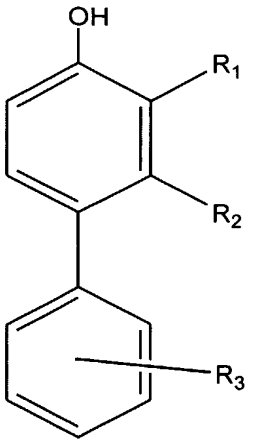
In a still further aspect of the invention, methods are provided for using the oral composition comprising at least one antimicrobial compound selected from Formulas IIIa-IIIc for reducing the presence of microorganisms in an oral cavity of an individual. The methods include administering into the oral cavity an effective amount of the oral composition containing the antimicrobial compounds selected from Formulas IIIa-IIIc.

Detailed Description of the Invention

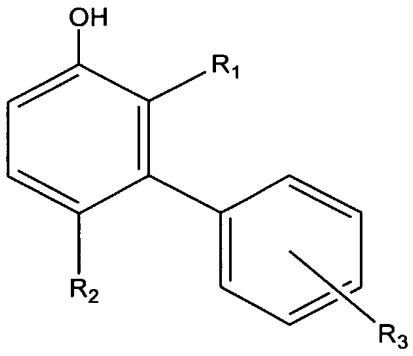
The present invention is directed to phenyl substituted phenol compounds which exhibit effective antimicrobial activities in a variety of compositions and applications while maintaining a positive safety profile desirable for human use. The antimicrobial activity and/or pharmaceutical properties of the compounds of the present invention are much improved over those exhibited by prior art antimicrobial compounds. Since the novel compounds are composed entirely of hydrocarbon constituents with a hydroxyl substitutent, such compounds are significantly safer than prior art antimicrobial compounds such as halogenated phenoxyphenols, for example. More specifically, the novel compounds include phenol substituted with at least one phenyl optionally substituted with alkyl group substitutents which substantially improves overall antimicrobial activity for effectively reducing the presence of microorganisms.

The present invention is further directed to the antimicrobial composition which is effective in treating various substrate surfaces including the oral cavity that may contain microorganisms. The antimicrobial composition is especially effective against microorganisms residing in the oral cavity responsible for bad breath, plaque and/or calculus, and the resulting tooth and gum diseases that may be caused thereby. The antimicrobial composition is effective yet is safe to use and is available in a variety of forms and antimicrobial applications and uses.

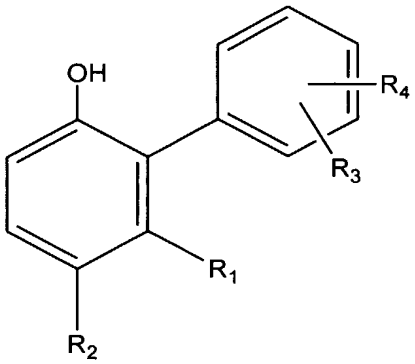
Accordingly, the present invention provides for phenyl substituted phenol compounds exhibiting antimicrobial activities which are represented by one of the following formulas:



Ia



Ib



Ic

wherein

R_1 and R_2 are each independently selected from the group consisting of hydrogen, an alkyl group optionally substituted with a cycloalkyl group, a hydroxyl group, or an aryl group; an alkenyl group; an alkoxy group; a cycloalkenyl group; an aryl group; benzyl optionally substituted with an alkyl group; and a cycloalkyl group wherein any one of which said groups may optionally be substituted with hydroxyl; and

R_3 is selected from the group consisting of hydrogen, an alkyl group optionally substituted with a hydroxyl group, an aryl group, benzyl, a benzyloxyl group, an alkoxy group, and a cycloalkyl group optionally substituted with hydroxyl;

R_4 is selected from the group consisting of hydrogen and an alkyl group optionally substituted with hydroxyl;

with the proviso that,

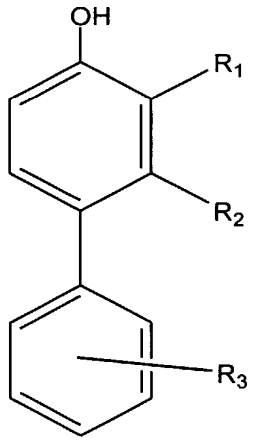
for compounds of Formula Ia, when R_1 is a C_{1-8} n-alkyl group or a C_{3-6} cycloalkyl group, each being optionally partially or fully substituted with a C_{3-6} cycloalkyl group or a C_{1-7} side chain

alkyl group, and R_2 is hydrogen, then R_3 is not selected from the group consisting of a C_{1-8} n-alkyl group and a C_{3-6} cycloalkyl group, each being optionally partially or fully substituted with a C_{3-6} cycloalkyl group or a C_{1-7} side chain alkyl group;

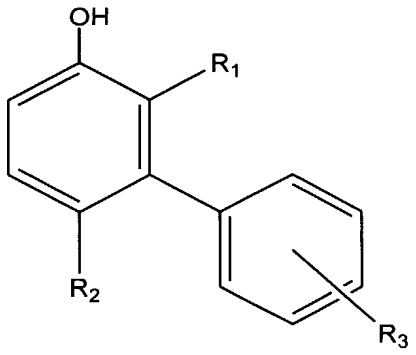
for compounds of Formulas Ia through Ic, when R_1 and R_2 are each hydrogen, then R_3 is not selected from the group consisting of a hydrogen, a 4-alkyl group, or a 2-benzyloxy group; and

for compounds of Formula Ic wherein each of R_1, R_3 and R_4 are hydrogen, then R_2 is not selected from the group consisting of a methyl group, an ethyl group or a tert-butyl group.

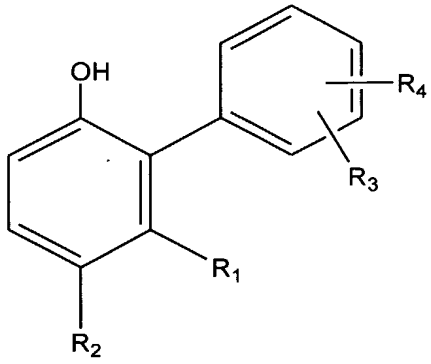
The present invention further provides for preferred compositions comprising an antimicrobial acceptable carrier and an antimicrobial effective amount of at least one antimicrobial compound selected from the following formulas:



IIa



IIb



IIc

wherein

R_1 and R_2 are each independently selected from the group consisting of hydrogen, an alkyl group optionally substituted with a hydroxyl group, a cycloalkyl group or an aryl group; an alkenyl group; an alkoxy group; a cycloalkenyl group; an aryl group; benzyl optionally substituted with an alkyl group; and a cycloalkyl group optionally substituted with hydroxyl;

R_3 is selected from the group consisting of hydrogen, a hydroxyl, an alkyl group, benzyl, and a cycloalkyl group optionally substituted with hydroxyl; and

R_4 is selected from the group consisting of hydrogen and an alkyl group optionally substituted with a hydroxyl;

with the proviso that,

for compounds of Formula IIa, when R_1 is a C_{1-8} n-alkyl group or a C_{3-6} cycloalkyl group, each being optionally partially or fully substituted with a C_{3-6} cycloalkyl group or a C_{1-7} side chain alkyl group, and R_2 is hydrogen, then R_3 is not selected from the group consisting of a C_{1-8} n-alkyl group and a C_{3-6} cycloalkyl group, each being optionally partially or fully substituted with a C_{3-6} cycloalkyl group or a C_{1-7} side chain alkyl group; and

for compounds of Formulas IIa through IIc, when R_1, R_2 and R_4 are each hydrogen, then R_3 is not hydrogen.

Compounds useful in the antimicrobial compositions of the present invention include, but are not limited to, 4-(tert-butyl)-2-(2-hydroxyphenyl)phenol, 4-ethyl-2-(2-hydroxyphenyl)phenol, 4-(4-hydroxybutyl)-2-(2-hydroxyphenyl)phenol, 4-(hydroxymethyl)-2-(2-hydroxyphenyl)anisole, 4-(hydroxymethyl)-2-(2-hydroxyphenyl)phenol, 2-(2-hydroxyphenyl)-4-benzylphenol, 4-ethyl-2-phenylphenol, 2-phenyl-4-propylphenol, 5-Isopropyl-biphenyl-2-ol, 4-[4-(tert-butyl)phenyl]phenol, 4-(1,1-dimethylethyl)-phenylphenol, 3-(4-tert-butylphenyl)phenol, 2-(4-tert-butylphenyl)phenol, (2-,4-diphenyl)phenol, (4-tert-butyl, 2-phenyl)phenol, 2-(4-tert-butylphenyl)phenol, and 3-phenylphenol.

Preferred for use in the antimicrobial compositions are 4-(tert-butyl)-2-(2-hydroxyphenyl)phenol, 4-ethyl-2-(2-hydroxyphenyl)phenol, 4-(4-hydroxybutyl)-2-(2-hydroxyphenyl)phenol, 4-(hydroxymethyl)-2-(2-hydroxyphenyl)anisole, 4-(hydroxymethyl)-2-(2-hydroxyphenyl)phenol, 2-(2-hydroxyphenyl)-4-benzylphenol, 4-ethyl-2-phenylphenol, 2-phenyl-4-propylphenol, 5-Isopropyl-biphenyl-2-ol, and 4-[4-(tert-butyl)phenyl]phenol.

Particularly preferred for use in the antimicrobial compositions are 4-(tert-butyl)-2-(2-hydroxyphenyl)phenol, 4-ethyl-2-(2-hydroxyphenyl)phenol, 4-(4-hydroxybutyl)-2-(2-hydroxyphenyl)phenol, 4-(hydroxymethyl)-2-(2-hydroxyphenyl)anisole, 4-(hydroxymethyl)-2-(2-hydroxyphenyl)phenol, and 2-(2-hydroxyphenyl)-4-benzylphenol.

The above antimicrobial compounds of Formulas IIa-IIc, are preferably incorporated in an antimicrobial composition of the present invention in an amount of about 0.0001 to 10%, more preferably from about 0.001 to 5 % by weight.

The present invention also provides a method of reducing the presence of microorganisms on a substrate comprising treating the substrate with an effective amount of at least one antimicrobial compound selected from Formulas IIa-IIc.

The antimicrobial compositions of the present invention may be incorporated into food products for use as food preservatives. Such food preservative compositions may comprise at least one compound selected from Formulas IIa-IIc and an edible carrier, which may be added to food products to prevent or delay spoilage or discoloration caused by microorganisms. The composition may further include other food preservative agents including, but not limited to benzoic acid, sodium benzoate, and calcium propionate.

The antimicrobial compounds selected from Formulas IIa-IIc employed in this invention may also be incorporated into ophthalmic compositions suitable for topical administration. Such compositions may include topical ocular fluids comprising at least one antimicrobial compound suspended or dissolved in a sterile, isotonic, typically aqueous pharmaceutically acceptable ocular carrier or vehicle. The ophthalmic compositions may also be prepared in the form of ointments or salves. Such ointments or salves typically comprise at least one antimicrobial compound having Formulas IIa-IIc suspended or dissolved in a sterile, pharmaceutically acceptable ointment or salve base such as, for example, mineral oil/white petroleum base.

The liquid formulation of ophthalmic compositions typically requires the presence of water under isotonic conditions, and such compositions are intended for external application to the eye (i.e. eye drops). The antimicrobial compounds of Formulas IIa-IIc may be insoluble in water or dispersion medium, and may be suspended through use of suspending or dispersing agents. The compounds of the present invention may further be dispersed by means of emulsifying agents or other suitable stabilizers as known in the art.

The ophthalmic composition may include about 0.0001 to 10%, more preferably from about 0.001 to 5 % by weight of the active antimicrobial compounds selected from Formulas IIa-IIc with the rest of the composition being the carrier and other materials known in the art as ophthalmological pharmaceutical ingredients or components. Such additional ingredients may include preservatives, solubilizers, emulsifying agents, surfactants, stabilizers, pH adjusting agents, buffers, isotonizers and the like. In ointment or salve compositions, anhydrous lanolin may also be included in the composition.

The antimicrobial compositions of the present invention may also be incorporated into products having a variety of vehicles for application to the skin or tissue surfaces including creams, lotions, foundations, cleansing lotions, soaps, shampoos, ointments, syrups and suspensions. Compositions may comprise, for example, aqueous or oily solutions or dispersions, oil-in-water or water-in-oil emulsions, pastes, gels or solids. Topically or orally acceptable carriers and excipients of use in such preparations will be well known to those skilled in the art.

The antimicrobial compositions of the present invention may further be included in products which are developed for the treatment of microorganism-induced conditions such as deodorant and/or antiperspirant preparations, antibacterial skin washes, anti-acne preparations, anti-athlete foot preparations, dental preparations, impregnated materials (e.g. wound dressings, sutures, and dental floss), pharmaceuticals, ophthalmic preparations and sterilants.

Typically, a deodorizing composition reduces or prevent body odor by reducing perspiration (e.g. often referred to as an antiperspirant composition) or the presence of microorganisms on the surface of the skin.

Antiperspirant compositions often comprise a metal salt, such as aluminium or zirconium salts which blocks the pores of the skin. Typically, such compositions, however, reduce perspiration by no more than 50%. It is well known that sweat is odorless until it has been degraded by the skin microflora. Typical deodorant compositions include ethanol and/or Triclosan (2',4,4'-trichloro,2-

hydroxy-diphenyl ether) which are a well known antimicrobial compounds. However, the deodorizing effect obtained with such deodorant compositions is transitory and shortly after application the concentration of microorganisms reaches previous levels.

The invention provides a deodorant composition for topical application to human skin comprising at least one antimicrobial compound selected from Formulas IIa-IIc in a cosmetically acceptable carrier in which the composition at least reduces the presence of microorganisms for a time greater than the transitory period.

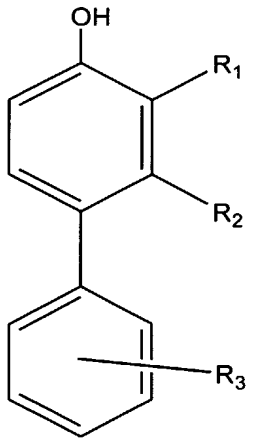
Such deodorant compositions in addition to containing the composition of the present invention contain a low molecular weight aliphatic alcohol, preferably containing up to 4 carbons and especially a monohydric alcohol such as ethanol, which can act in combination with the antimicrobial compounds selected from Formulas IIa-IIc to provide an effective deodorant composition. The amount of the alcohol in the composition is typically selected within the range of from about 10 to 80% by weight, preferably from about 30 to 70% by weight.

The deodorant composition according to the present invention may also comprise other materials commonly found in deodorant or antiperspirant compositions. In practice, the present composition usually contains at least one cosmetically acceptable vehicle in addition to the antimicrobial compounds selected from Formulas IIa-IIc alone or in combination with an alcohol. The topically acceptable carrier may comprise a liquid vehicle such as an alcohol as described hereinbefore, in addition to, water, a hydrophobic vehicle which may for example be a volatile or non-volatile silicone oil, a liquid hydrocarbon, a water-insoluble alcohol, an aliphatic ether, an aliphatic or aromatic ester. The carrier is typically present in an amount of from about 10 to 80% by weight based on the total weight of the composition.

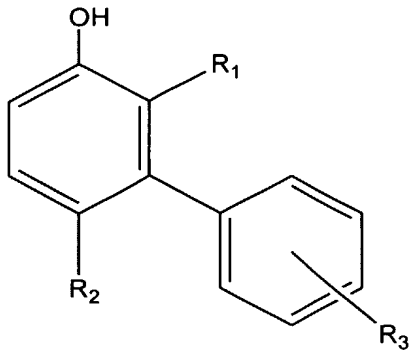
The composition of the present invention may contain one or more conventional deodorant active compounds as known to those of ordinary skill in the art, in an amount of from about 0 to 5% by weight. Other additives may include perfumes in an amount of from about 0 to 2% by weight, antiperspirant actives such as aluminium or zirconium compounds in an amount of from about 0 to

40% by weight, preferably from about 5 to 28 % by weight, skin softening compounds such as silicone oils or solid silicone polymers, in an amount of from about 0 to 20% by weight, coloring compounds in an amount of from about 0 to 2% by weight, humectants, such as sorbitol or glycerol, in an amount of from about 0 to 10% by weight, thickening compounds such as starches or cellulose derivatives, in an amount from about 0 to 5% by weight, gellants such as dibenzoyl sorbitol, hydroxystearic acid, stearyl alcohol, or amide derivatives of tricarboxylic acids, in an amount of from about 0 to 15% by weight, suspension compounds, such as clays or silicas, in an amount of up to about 5% by weight, structurants such as silicone elastomers or silicone or hydrocarbon waxes, in an amount of about 0 to 15% by weight; propellants, such as hydrocarbons having a boiling point of below 10EC, e.g. butane and propane isomers, in an amount of from about 30 to 95% by weight, and other cosmetic adjuncts conventionally employed in such compositions. Where water and a hydrophobic material is present, the composition preferably contains an emulsifier/system such as polyethoxylate ethers or esters. The use of such substances and the proportions in which they are incorporated depend on the form of the composition which may be an aerosol, stick, roll-on, gel, lotion, cream, ointment, powder, suspension or soap.

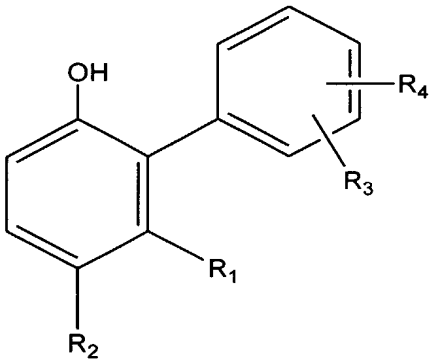
More preferred compositions include those represented for use in an oral cavity comprising an orally acceptable carrier and an antimicrobial effective amount of at least one antimicrobial compound selected from the following formulas:



IIIa



IIIb



IIIc

wherein

R_1 and R_2 are each independently selected from the group consisting of hydrogen, an alkyl group optionally substituted with a a hydroxyl, cycloalkyl group or an aryl group; an alkenyl group; an alkoxy group; a cycloalkenyl group; an aryl group; benzyl optionally substituted with an alkyl group; and a cycloalkyl group wherein any one of which said groups may optionally be substituted with hydroxyl; and

R_3 is selected from the group consisting of hydrogen, a hydroxyl, an alkyl group, a benzyl, a benzyloxy group, an alkoxy group and a cycloalkyl group optionally substituted with hydroxyl;

R_4 is selected from the group consisting of a hydrogen and an alkyl group optionally substituted with hydroxyl;

with the proviso that,

for compounds of Formula IIIa, when R_1 is a C_{1-8} n-alkyl group or a C_{3-6} cycloalkyl group, each being optionally partially or fully substituted with a C_{3-6} cycloalkyl group or a C_{1-7} side chain alkyl group, and R_2 is hydrogen, then R_3 is not selected from the group consisting of a C_{1-8} n-alkyl

group and a C_{3-6} cycloalkyl group, each being optionally partially or fully substituted with a C_{3-6} cycloalkyl group or a C_{1-7} side chain alkyl group; and

for compounds of Formula IIIa, when R_1, R_2 and R_4 are each hydrogen, then R_3 is not a hydrogen.

Compounds useful for oral compositions include, but are not limited to, 4-(tert-butyl)-2-(2-hydroxyphenyl)phenol, 4-ethyl-2-(2-hydroxyphenyl)phenol, 4-(4-hydroxybutyl)-2-(2-hydroxyphenyl)phenol, 4-(hydroxymethyl)-2-(2-hydroxyphenyl)anisole, 4-(hydroxymethyl)-2-(2-hydroxyphenyl)phenol, 2-(2-hydroxyphenyl)-4-benzylphenol, 4-ethyl-2-phenylphenol, 2-phenyl-4-propylphenol, 5-Isopropyl-biphenyl-2-ol, 4-[4-(tert-butyl)phenyl]phenol, 4-(1,1-dimethylethyl)-phenylphenol, 3-(4-tert-butylphenyl)phenol, 2-(4-tert-butylphenyl)phenol, (2-,4-diphenyl)phenol, (4-tert-butyl, 2-phenyl)phenol, 2-(4-tert-butylphenyl)phenol, and 3-phenylphenol.

Preferred for use in oral compositions are 4-(tert-butyl)-2-(2-hydroxyphenyl)phenol, 4-ethyl-2-(2-hydroxyphenyl)phenol, 4-(4-hydroxybutyl)-2-(2-hydroxyphenyl)phenol, 4-(hydroxymethyl)-2-(2-hydroxyphenyl)anisole, 4-(hydroxymethyl)-2-(2-hydroxyphenyl)phenol, 2-(2-hydroxyphenyl)-4-benzylphenol, 4-ethyl-2-phenylphenol, 2-phenyl-4-propylphenol, 5-Isopropyl-biphenyl-2-ol, and 4-[4-(tert-butyl)phenyl]phenol

Particularly preferred for use in oral compositions are 4-(tert-butyl)-2-(2-hydroxyphenyl)phenol, 4-ethyl-2-(2-hydroxyphenyl)phenol, 4-(4-hydroxybutyl)-2-(2-hydroxyphenyl)phenol, 4-(hydroxymethyl)-2-(2-hydroxyphenyl)anisole, 4-(hydroxymethyl)-2-(2-hydroxyphenyl)phenol, and 2-(2-hydroxyphenyl)-4-benzylphenol.

The antimicrobial compounds selected from Formulas IIIa-IIIc may be present in an oral composition of the present invention preferably in an amount of from about 0.0001 to 10%, more preferably from about 0.001 to 5% by weight.

The present invention further provides a method of reducing microorganisms in an oral cavity which comprises administering to the oral cavity an oral composition having an effective amount of at least one antimicrobial compound selected from Formulas IIIa-IIIc.

The use of the antimicrobial compositions according to the invention in oral compositions is particularly advantageous because they provide effective results against a broad range of microorganisms known to be present in the oral cavity. The oral compositions may take the form of bulk liquid solutions or suspensions, semisolid pastes or gels, or bulk powders for convenient application to the surface of the oral cavity.

Oral compositions which contain antimicrobial compounds of the present invention may be in the form of mouthwashes, gargles, dentifrices, anti-plaque compositions and as a general antiseptic composition, for example, in the form of denture cleansing tablets or solutions. The oral compositions of the present invention may, if desired, further comprise at least one additional active ingredient and formulations containing such, as conventionally used in the art. These include, for example, anti-plaque agents such as bromochlorophene, triclosan, cetylpyridinium chloride, chlorhexidine salts, and essential oils such as thymol, menthol, and the like, fluoride ion sources such as sodium fluoride, sodium monofluorophosphate and amine fluorides, anti-tartar compounds such as zinc salts, preferably zinc citrate, and water soluble pyrophosphate salts, preferably alkali metal pyrophosphates, and desensitizing agents which reduce tooth sensitivity including potassium salts such as potassium nitrate and potassium chloride and strontium salts such as strontium chloride and strontium acetate.

One particular formulation comprising essential oils is sold commercially as LISTERINE® which composition is exemplified in Pan et al. (U.S. Pat. No. 6,121,315), and which reference includes effective essential oil formulations having anti-plaque activity. The contents of U.S. Pat. No. 6,121,315 is hereby incorporated by reference in its entirety. The essential oil formulation, optionally contained in the oral compositions of the present invention, preferably comprises from about 0.005 % to 0.5 % by weight of thymol, from about 0.005 % to 0.5 % by weight of menthol, from about 0.005 % to 0.5 % by weight of eucalyptol, and from about 0.005 % to 0.5 % by weight of methyl salicylate.

The compositions according to the invention may alternatively be provided in concentrated form, for example as a powder, anhydrous solution or effervescent tablet formulation, suitable for dilution in water prior to use as a sterilant of, for example, dental instruments. One preferred use of the anti-microbial compositions of the invention is as toothbrush sanitizers, designed to reduce microbiological contamination of toothbrush heads, for example by overnight soaking as needed, typically every 1 to 14 days of use. A substantial reduction in microorganism contamination may be achieved in this way without significant adverse effects on the toothbrush or other dental instrument.

Fluoride ions may also be included in the oral compositions of the present invention. Fluoride ions are implicated in the prevention of dental caries and may also serve as a tooth-hardening agent. An amount of fluoride ions suitable for use in an oral composition of the present invention is from 25 ppm to 5,000 ppm.

Fluoride ion producing compounds vary in degree of water solubility. They release fluoride ions in water and do not generally react with other compounds of the oral composition. Among the fluoride ion producing compounds are inorganic fluoride salts, such as soluble alkali metal, alkaline earth metal salts, for example, sodium fluoride, potassium fluoride, ammonium fluoride, calcium fluoride, cuprous fluoride, zinc fluoride, barium fluoride, sodium monofluorophosphate, aluminum mono-and di-fluorophosphate and sodium calcium fluorophosphate. Alkali metal and tin fluorides, such as sodium and stannous fluorides, sodium monofluorophosphate (MFP) and mixtures thereof, are preferred.

The amount of fluoride ion producing compound is dependent upon the type of compound, its solubility in water, and the type of oral composition. A non-toxic amount of such compound is generally in the range from about 0.0005 to 3.0% by weight based on the total weight of the oral composition. Any suitable minimum amount of such compounds may be used, but it is preferable to employ a sufficient amount of the fluoride ion producing compounds to provide from about 300 to 2,000 ppm, more preferably from about 800 to about 1,500 ppm of fluoride ion to the oral cavity.

Typically, for sodium fluoride, the desired amount up to about 2% by weight, based on the total weight of the composition, and preferably in an amount of from about 0.05 to 1%, more preferably from about 0.2 to 0.35% by weight. Typically for sodium monofluorophosphate, the compound is desirably present in an amount of from about 0.1 to 3%, more preferably about 0.76% by weight.

The oral composition of the present invention may be in the form of a solution such as a mouthrinse, in the form of a solid or semi-solid such as a toothpaste, a gel dentifrice (which may contain from about 0 to 75% by weight of a polishing agent), a chewing gum, or a solid lozenge or the like.

Oral gel preparations typically contain a siliceous polishing material including crystalline silica having particle sizes of up to 5 microns, silica gel, colloidal silica or complex amorphous alkali metal aluminosilicate or combinations thereof. When visually clear or opacified gels are employed, a polishing agent of colloidal silica or alkali metal aluminosilicate complexes (that is, silica containing alumina combined in its matrix) are particularly useful, since they are consistent with gel-like texture and have refractive indices close to the refractive indices of gelling agent-liquid (including water and/or humectant) systems commonly used in dentifrices.

Where the oral composition of the present invention is a gel or paste, an orally acceptable carrier, including a water-phase with humectant which is preferably glycerine or sorbitol or an alkylene glycol such as polyethylene glycol or propylene glycol is present. Where water is typically present in an amount of from about 15 to 40% by weight and glycerine, sorbitol and/or the alkylene glycol (preferably propylene glycol) are preferably in an amount of from about 20 to 75% by weight, preferably about 25 to 60% by weight based on the total weight of the composition.

When the oral composition is substantially semi-solid or pasty in character, such as a toothpaste (dentifrice), the orally acceptable carrier of the dentifrice may contain a dentally acceptable polishing material such as sodium bicarbonate, sodium metaphosphate, potassium metaphosphate, tricalcium phosphate, dihydrated dicalcium phosphate, anhydrous dicalcium

phosphate, calcium pyrophosphate, calcium carbonate, aluminum silicate, hydrated alumina, silica, bentonite, and mixtures thereof alone or with minor amounts of hard polishing material such as calcined alumina and/or zirconium silicate. Preferred polishing materials include sodium bicarbonate, silica, sodium metaphosphate, dicalcium phosphate, calcium pyrophosphate and hydrated alumina.

The polishing material is generally present in the oral composition in an amount of from about 10% to 75% by weight, preferably from about 10% to 30% by weight in a gel, and preferably from about 25% to 75% by weight in a cream or paste.

Toothpastes or dental cream dentifrices as well as gel dentifrices typically contain a natural or synthetic thickener or gelling agent in an amount of from about 0.1 to 10% by weight, preferably from about 0.5 to 5% by weight.

Suitable thickeners or gelling agents include Irish moss, iota-carrageenan, kappa-carrageenan, gum tragacanth, starch, polyvinylpyrrolidone, hydroxyethyl propyl cellulose, hydroxybutyl methyl cellulose, hydroxypropyl methyl cellulose, hydroxyethyl cellulose and sodium carboxymethyl cellulose.

Where the oral composition is a liquid such as a mouthwash or rinse, the liquid carrier is typically a water-alcohol mixture. Generally, the weight ratio of water to alcohol is in the range of from about 3:1 to 10:1 and preferably from about 4:1 to 6:1. The alcohol is a non-toxic alcohol such as ethanol or isopropanol. A humectant such as glycerin, sorbitol or an alkylene glycol such as polyethylene glycol or preferably propylene glycol may be present in an amount of from about 10 to 30% by weight. Mouthrinses typically contain about 50 to 85% of water, from about 0 to 20% by weight of a non-toxic alcohol and from about 10 to 40% by weight of a humectant.

Organic surface-active agents may be used in the compositions of the present invention to achieve increased antimicrobial action, assist in achieving thorough and complete dispersion of the antimicrobial compounds of Formulas IIIa-IIIc throughout the oral cavity. The organic surface-active

material is preferably anionic, nonionic or ampholytic in nature, and is a detersive material which imparts to the composition detersive and foaming properties. Suitable examples of anionic surfactants are water-soluble salts of higher fatty acid monoglyceride monosulfates, such as the sodium salt of the monosulfated monoglyceride of hydrogenated coconut oil fatty acids, higher alkyl sulfates such as sodium lauryl sulfate, alkyl aryl sulfonates such as sodium dodecyl benzene sulfonate, higher alkyl sulfoacetates, higher fatty acid esters of 1,2-dihydroxy propane sulfonate, and the substantially saturated higher aliphatic acyl amides of lower aliphatic amino carboxylic acid compounds, such as those having 12 to 16 carbons in the fatty acid, alkyl or acyl radicals and alkoyl taurines, and the like. Examples of such compounds include N-lauroyl sarcosine, and the sodium, potassium and ethanolamine salts of N-lauroyl, N-myristoyl, or N-palmitoyl sarcosine which are substantially free from soap or similar higher fatty acid material as well as N-methyl-N-cocoyl (or oleoyl or palmitoyl) taurines. The use of sarcosinate compounds in the oral compositions of the present invention is typically advantageous since these materials exhibit a prolonged and marked effect in the inhibition of acid formation in the oral cavity due to carbohydrate breakdown in addition to exerting some reduction in the solubility of tooth enamel in acid solutions.

Examples of water-soluble nonionic surfactants are condensation products of ethylene oxide with various reactive hydrogen-containing compounds reactive therewith having long hydrophobic chains (e.g. aliphatic chains of about 12 to 20 carbon atoms), which condensation products ("ethoxamers") contain hydrophilic polyoxyethylene moieties, such as condensation products of poly (ethylene oxide) with fatty acids, fatty alcohols, fatty amides, polyhydric alcohols (e.g. sorbitan monostearate) and polypropyleneoxide.

Examples of polyoxamers useful in the practice of the present invention include block copolymers of polyoxyethylene and polyoxypropylene having an average molecular weight of from about 3000 to 5000 and a preferred average molecular weight of from about 3500 to 4000, and containing from about 10 to 80% by weight of hydrophilic polyoxyethylene groups of the block copolymer.

Any suitable flavoring or sweetening agent may also be employed. Examples of suitable flavoring agents are flavoring oils, e.g. oil of spearmint, peppermint, wintergreen, sassafras, clove, sage, eucalyptus, cinnamon, lemon, and orange, and methyl salicylate. Suitable sweetening agents include sucrose, lactose, maltose, xylitol, sodium cyclamate, perillartine, aspartyl phenyl alanine methyl ester, sucralose, saccharine and the like. The flavoring and sweetening agents may each or together comprise from about 0.1% to 5% by weight or more of the oral composition.

Desensitizing agents used to diminish teeth sensitivity such as strontium chloride, potassium nitrate and potassium citrate may also be included in the oral compositions of the present invention at concentrations of from about 0.1 to 10% by weight.

Various other materials may be incorporated in the oral compositions of the invention including whitening agents such as urea peroxide and hydrogen peroxide, preservatives, such as sodium benzoate, chlorophyll compounds and/or ammoniated compounds such as urea, diammonium phosphate, and mixtures thereof. These adjuvants, when present, are incorporated in the compositions in amounts which do not substantially adversely affect the desired properties.

The oral compositions of the present invention may be prepared by suitably mixing the ingredients. By way of example, in the preparation of a mouthrinse, the antimicrobial compound of Formulas IIIa-IIIc may be dispersed in a mixture containing for example, alcohol, humectant, surfactant, and salts such as sodium fluoride and potassium phosphate, and a flavoring is then added and the resulting combination mixed thoroughly. Dentifrices are prepared in a similar manner with the addition, typically, of a thickener and a polishing agent.

The oral compositions of the present invention may be incorporated into lozenges, or in chewing gum or other products, e.g. by stirring into a warm gum base or coating the outer surface of a gum base, illustrative of which may be mentioned jelutone, rubber latex, vinylite resins, and the like, desirably with conventional plasticizers or softeners, sugar or other sweeteners or carbohydrates such as glucose, sorbitol and the like.

The vehicle or carrier for a tablet or lozenge is desirably a non-cariogenic solid water-soluble polyhydric alcohol (polyol) such as mannitol, xylitol, sorbitol, malitol, a hydrogenated starch hydrolysate, Lycasin, hydrogenated glucose, hydrogenated disaccharides or hydrogenated polysaccharides, in an amount of from about 90 to 98% by weight. Solid salts such as sodium bicarbonate, sodium chloride, potassium bicarbonate or potassium chloride may totally or partially replace the polyol carrier.

Tableting lubricants, in minor amounts of from about 0.1 to 5% by weight, may be incorporated into the tablet or lozenge formulation to facilitate the preparation of both the tablets and lozenges. Suitable lubricants include vegetable oils such as coconut oil, magnesium stearate, aluminum stearate, talc, starch and Carbowax.

Lozenge formulations contain about 2% gum as a barrier agent to provide a shiny surface as opposed to a tablet which has a smooth finish. Suitable non-cariogenic gums include kappa carrageenan, carboxymethyl cellulose, hydroxyethyl cellulose, and the like.

The lozenge or tablet may optionally be coated with a coating material such as waxes, shellac, carboxymethyl cellulose, polyethylene/maleic anhydride copolymer or kappa-carrageenan to further increase the time it takes the tablet or lozenge to dissolve in the mouth. The uncoated tablet or lozenge is slow dissolving, providing a sustained release rate of active ingredients of about 3 to 5 minutes. Accordingly, the solid dose tablet and lozenge composition of this invention affords a relatively longer time period of contact of the teeth in the oral cavity with the active ingredients.

The foregoing discussion discloses and describes merely exemplary embodiments of the present invention. One skilled in the art will readily recognize from such discussion that various changes, modifications and variations can be made therein without departing from the spirit and scope of the invention as defined in the following claims.

EXAMPLE 1

Mouthrinse Composition Containing Antimicrobial Compounds

of Formulas IIIa-IIIc

A mouthrinse composition containing the ingredients and the amounts shown in Table 1 is prepared by mixing the alcohol soluble ingredients 2 and 3 with ethanol. Water is added to the mixture. Water soluble ingredients 4 through 9 are then added and blended thoroughly to the mixture. About 1000 ml of water is then added to the mixture to adjust the final volume to yield the mouthrinse composition.

Table 1

Ingredients	% by weight
1) Alcohol, USP	15
2) Antimicrobial Agents of Formula (II)	0.05
3) Flavoring oil	0.1
4) Glycerine	3
5) Sodium lauryl methyl cocoyl taurate	0.3
6) Sodium citrate	0.08
7) Citric acid	0.02
8) Saccharin sodium	0.1
9) FD&C Green #3	0.0002
10) Water, USP	QS to 100

EXAMPLE 2

Dentifrice Composition Containing Antimicrobial Compounds

of Formulas IIIa-IIIc

A dentifrice composition containing the ingredients and the amounts shown in Table 2 is prepared by combining water, a portion of the humectant, the sweetener, the fluoride, and the water soluble buffers together. The remainder of the humectant is separately combined with the gum and then added to the initial mixture. Titanium oxide and silicas are blended and then added to the mixture. The colorant, flavor oil, antimicrobial compounds of Formulas IIIa-IIIc and the surfactant are added and blended with the mixture to yield the dentrifice composition.

Table 2

Ingredients	% by weight
1) Glycerine	6
2) Sodium carboxymethylcellulose	1.2
3) Sorbitol	40
4) Sodium monofluoriphosphate, USP	0.76
5) Saccharin sodium	1
6) Sodium phosphate, dibasic	0.03
7) Sodium phosphate, monobasic	0.25
8) Silicon dioxide, hydrated	15
9) Titanium dioxide	0.2
10) Flavor oil	2
11) Antimicrobial Agents of Formula (II)	0.5
12) FD&C Green #3	0.0002
13) Water, deionized	QS to 100

EXAMPLE 3

Deodorant Composition Containing Antimicrobial

Compounds of Formulas IIa-IIc

A deodorant composition containing the ingredients and the amounts shown in Table 3 is prepared by mixing together the polar solvent, volatile nonpolar solvent, and the antimicrobial compounds of Formulas IIa-IIc. Gellants is added and agitated. The mixture is heated to a temperature in the range from about 75E to 100E C until the gellants melted and formed a substantially clear and translucent liquid. The resulting liquid mixture is slightly cooled prior to adding the fragrance. The resulting liquid mixture is poured into a suitable container and cooled thus yielding a solid form deodorant composition.

Table 3

Ingredients	% by weight
1) Propylene glycol	30
2) Glycerine	2.5
3) Butyl stearate	20
4) Antimicrobial Agents of Formula (I)	0.5
5) Propylene glycol monostearate	15
6) Water	32

EXAMPLE 4

Antibacterial Soap Composition Containing

Antimicrobial Compounds of Formulas IIa-IIc

An antibacterial soap composition containing the ingredients and the amounts shown in Table 4 is prepared by agitating and mixing the ingredients for thorough blending.

Table 4

Ingredients	% by weight
1) Sodium lauryl sulfate	67
2) Cocamidopropyl betaine	15

3) Glycerine	1
4) Propylene glycol	1
5) Antimicrobial Agents of Formula (I)	1
6) Fragrance	0.2
7) Water	QS to 100

EXAMPLE 5

Antibacterial Cream or Ointment Composition Containing

Antimicrobial Compounds of Formulas IIa-IIc

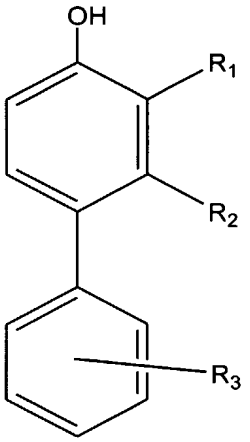
An antibacterial cream or ointment composition containing the ingredients and amounts shown in Table 5 is prepared by dissolving the antimicrobial compounds of Formulas IIa-IIc into the solvent and surfactant ingredients. The hydrophobic ingredients are then added to the resulting mixture and blended. The resulting mixture forms an emulsion having a uniform creamy consistency.

Table 5

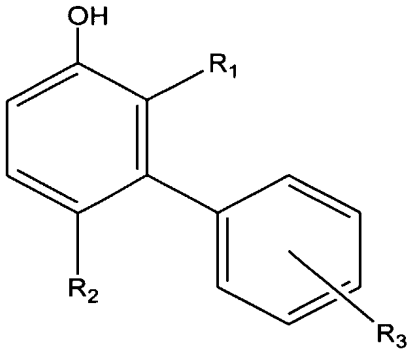
Ingredients	% by weight
1) Glycerine	6
2) Propylene glycol	5.5
3) Sodium lauryl sulfate	1
4) Cetyl alcohol	4.5
5) Cetyl palmitate	4
6) Steric alcohol	4.5
7) Steric acid	4
8) White petrolatum	5
9) Antimicrobial Agents of Formula (I)	1
10) Water, deionized	64.5

What is Claimed is:

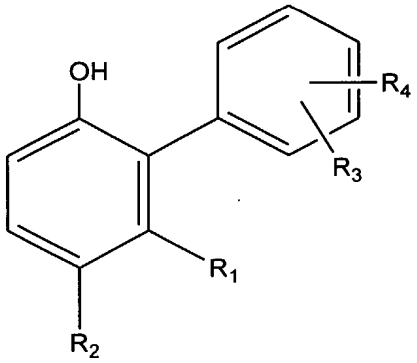
1. A compound selected from the following formulas:



Ia



Ib



Ic

wherein

R_1 and R_2 are each independently selected from the group consisting of hydrogen, an alkyl group optionally substituted with a cycloalkyl group, a hydroxyl group, or an aryl group; an alkenyl group; an alkoxy group; a cycloalkenyl group; an aryl group; benzyl optionally substituted with an alkyl group; and a cycloalkyl group wherein any one of which said groups can optionally be substituted with a hydroxyl; and

R_3 is selected from the group consisting of hydrogen, an alkyl group optionally substituted with a hydroxyl, an aryl group, a benzyl, a benzyloxyl group, an alkoxy group, and a cycloalkyl group optionally substituted with hydroxyl;

R_4 is selected from the group consisting of hydrogen and an alkyl group optionally substituted with a hydroxyl;

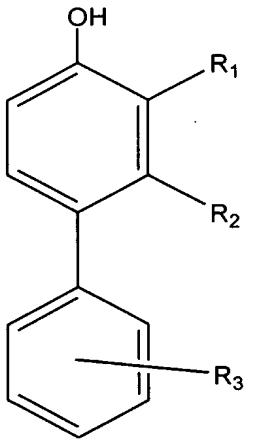
with the proviso that,

for compounds of Formula Ia, when R_1 is a C_{1-8} n-alkyl group or a C_{3-6} cycloalkyl group, each being optionally partially or fully substituted with a C_{3-6} cycloalkyl group or a C_{1-7} side chain alkyl group, and R_2 is hydrogen, then R_3 is not selected from the group consisting of a C_{1-8} n-alkyl group and a C_{3-6} cycloalkyl group, each being optionally partially or fully substituted with a C_{3-6} cycloalkyl group or a C_{1-7} side chain alkyl group;

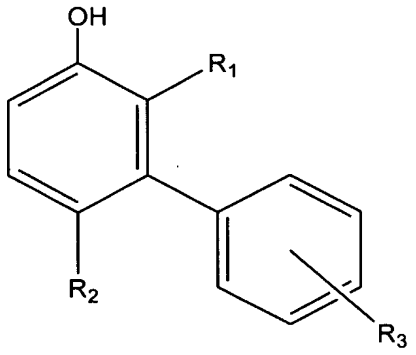
for compounds of Formulas Ia through Ic, when R_1 and R_2 are each hydrogen, then R_3 is not selected from the group consisting of a hydrogen, a 4-alkyl group, or a 2-benzyloxy group; and

for compounds of Formula Ic, when R_1, R_3,and R_4 are each a hydrogen, then R_2 is not selected from the group consisting of hydrogen, a methyl group, ethyl group or a tert-butyl group.

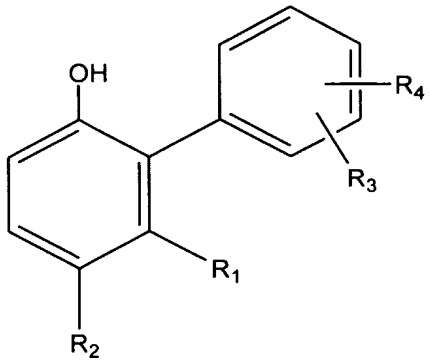
2. An antimicrobial composition comprising an antimicrobial acceptable carrier and an effective antimicrobial amount of at least one compound selected from the following formulas:



IIa



IIb



IIc

wherein

R_1 and R_2 are each independently selected from the group consisting of hydrogen, an alkyl group optionally substituted with a hydroxyl, a cycloalkyl group or an aryl group; an alkenyl group; an alkoxy group; a cycloalkenyl group; an aryl group; benzyl optionally substituted with an alkyl group; and a cycloalkyl group wherein any one of which said groups can optionally be substituted with hydroxyl; and

R_3 is selected from the group consisting of hydrogen, a hydroxyl, an alkyl group, a benzyl group, an alkoxy group and a cycloalkyl group optionally substituted with hydroxyl;

R_4 is selected from the group consisting of a hydrogen and an alkyl group optionally substituted with a hydroxyl;

with the proviso that,

for compounds of Formula IIa, when R_1 is a C_{1-8} n-alkyl group or a C_{3-6} cycloalkyl group, each being optionally partially or fully substituted with a C_{3-6} cycloalkyl group or a C_{1-7} side chain alkyl group, and R_2 is hydrogen, then R_3 is not selected from the group consisting of a C_{1-8} n-alkyl group and a C_{3-6} cycloalkyl group, each being optionally partially or fully substituted with a C_{3-6} cycloalkyl group or a C_{1-7} side chain alkyl group;

for compounds of Formulas IIa through IIb, when each of R_1 and R_2 is hydrogen, then R_3 is not a hydrogen; and

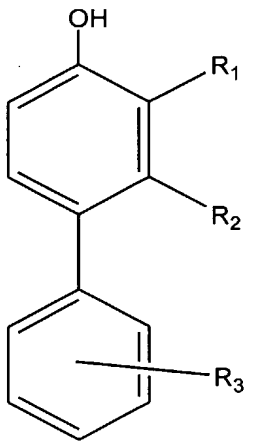
for compounds of Formulas IIc, when each of R_1, R_2, and R_4 is hydrogen, then R_3 is not a hydrogen.

3. An antimicrobial composition according to anyone of the preceding Claims, wherein R2 is selected from the group consisting of tert-butyl, benzyl, hexyloxy, cyclohex-2-enyl, cyclohexyl, 2-cyclohexylethyl, 1-methyl-1-ethylpropyl, ethyl, propyl, 5-hydroxypentyl, isopropyl, 1,1-dimethylpropyl, cyclopentyl, 1-methylbutyl, 2-hydroxycyclopentyl and 3-hydroxycyclopentyl.

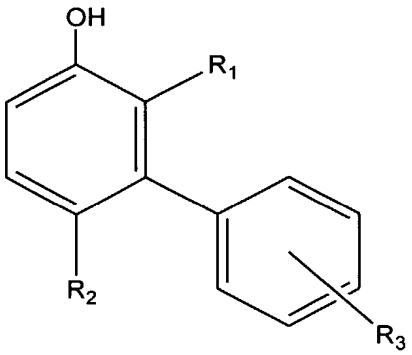
4. An antimicrobial composition according to anyone of the preceding Claims, wherein the antimicrobial effective carrier is selected from the group consisting of water, saline, alcohol, glycerin, propylene glycol, mineral oil, petrolatum, and mixtures thereof.

5. An antimicrobial composition according to any one of the preceding Claims, wherein the antimicrobial effective amount is from about 0.0001 to 10% by weight of the total weight of the antimicrobial composition.

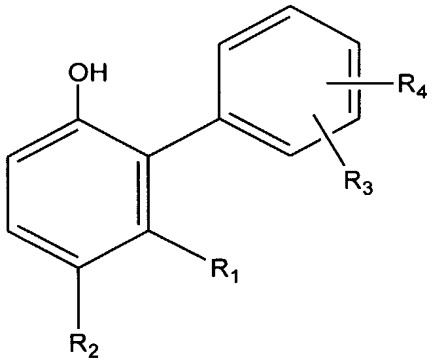
6. An oral composition comprising an orally acceptable carrier and an effective antimicrobial amount of at least one compound selected from the following formulas:



IIIa



IIIb



IIIc

wherein

R_1 and R_2 are each independently selected from the group consisting of hydrogen, an alkyl group optionally substituted with a hydroxyl group, a cycloalkyl group or an aryl group; an alkenyl group; an alkoxy group; a cycloalkenyl group; an aryl group; benzyl optionally substituted with an alkyl group; and a cycloalkyl group wherein any one of said groups can optionally be substituted with a hydroxyl group; and

R_3 is selected from the group consisting of hydrogen, a hydroxyl group, an alkyl group, a benzyl group, a benzyloxy group, an alkoxy group,and a cycloalkyl group optionally substituted with hydroxyl;

R_4 is selected from the group consisting of a hydrogen and an alkyl group optionally substituted with a hydroxyl;

with the proviso that,

for compounds of Formula IIIa, when R_1 is a C_{1-8} n-alkyl group or a C_{3-6} cycloalkyl group, each being optionally partially or fully substituted with a C_{3-6} cycloalkyl group or a C_{1-7} side chain alkyl group, and R_2 is hydrogen, then R_3 is not selected from the group consisting of a C_{1-8} n-alkyl group and a C_{3-6} cycloalkyl group, each being optionally partially or fully substituted with a C_{3-6} cycloalkyl group or a C_{1-7} side chain alkyl group;

for compounds of Formulas IIIa through IIIb, when each of R_1 and R_2 is hydrogen, then R_3 is not a hydrogen; and

for compounds of Formulas IIIc, when each of R_1, R_2, and R_4 is hydrogen, then R_3 is not a hydrogen.

7. An oral composition according to anyone of the preceding Claims, wherein the compound has the Formula IIIa wherein each of R_2 and R_3 is hydrogen, and R_1 is selected from the group consisting of an alkyl group substituted with an aryl group; a cycloalkenyl group; benzyl substituted with an alkyl group; a cycloalkyl group optionally substituted with hydroxyl; and an aryl group optionally substituted with an alkyl group.

8. An oral composition according to anyone of the preceding Claims, wherein the compound has the Formula IIIa wherein R_2 is hydrogen, and R_3 is tert-butyl, and R_1 is selected from the group consisting of hydrogen and phenyl.

9. An oral composition according to anyone of the preceding Claims, wherein the compound has the Formula IIIa wherein each of R_1 and R_2 is hydrogen, and R_3 is selected from the group consisting of an alkyl group and a cycloalkyl group optionally substituted with hydroxyl.

10. An oral composition according to anyone of the preceding Claims, wherein the compound has Formula IIIc wherein each of R_1, R_3, and R_4 is hydrogen and R_2 is selected from the group consisting of an alkyl group optionally substituted with a cycloalkyl or a hydroxyl; a benzyl; an alkoxy group; a cycloalkenyl group; a cycloalkyl group optionally substituted with a hydroxyl.

11. An oral composition according to anyone of the preceding Claims, wherein the compound has Formula IIIc wherein each of R_1, R_2, and R_4 is hydrogen, and R_3 is selected from the group consisting of a benzyloxy group or an alkyl group.

12. An oral composition according to anyone of the preceding Claims, wherein the compound has the Formula IIIc wherein each of R_1 and R_4 is hydrogen, R_3 is a hydroxyl, and R_2 is a benzyl group, or an alkyl group optionally substituted with a hydroxyl.

13. An oral composition according to anyone of the preceding Claims, wherein the compound has the formula IIIc wherein each of R_1 and R_2 is hydrogen, R_3 is an alkoxy group, and R_4 is an alkyl group optionally substituted with hydroxyl.

14. An oral composition according to anyone of the preceding Claims, wherein the compound has the Formula IIIb wherein each of R_1 and R_2 is hydrogen, and R_3 is selected from the group consisting of an alkyl group and a cycloalkyl group optionally substituted with hydroxyl.

15. An oral composition according to anyone of the preceding Claims, wherein the compound has the Formula IIIb wherein R_1 is hydrogen, R_2 is phenyl, and R_3 is an alkyl group.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/IB 01/02208

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07C39/15 A61K7/06 A61K31/05

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 723 500 A (STRINGER ET AL) 3 March 1998 (1998-03-03) column 3 -column 4 claims	1-15
X	WO 97 10800 A (COLGATE PALMOLIVE CO) 27 March 1997 (1997-03-27) claims	1-15

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
8 April 2002	18/04/2002

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Van Geyt, J

INTERNATIONAL SEARCH REPORT

Information on patent family members

Ir tional Application No
PCT/IB 01/02208

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5723500 A	03-03-1998	US 6096293 A	01-08-2000
		US 5912274 A	15-06-1999
		AU 708974 B2	19-08-1999
		AU 7075996 A	09-04-1997
		BR 9610562 A	06-07-1999
		CA 2232838 A1	27-03-1997
		CN 1200025 A	25-11-1998
		EP 0852486 A2	15-07-1998
		JP 11511473 T	05-10-1999
		RU 2170079 C2	10-07-2001
		WO 9710800 A2	27-03-1997
WO 9710800 A	27-03-1997	AU 708974 B2	19-08-1999
		AU 7075996 A	09-04-1997
		BR 9610562 A	06-07-1999
		CA 2232838 A1	27-03-1997
		CN 1200025 A	25-11-1998
		EP 0852486 A2	15-07-1998
		JP 11511473 T	05-10-1999
		RU 2170079 C2	10-07-2001
		WO 9710800 A2	27-03-1997
		US 6096293 A	01-08-2000
		US 5723500 A	03-03-1998
		US 5912274 A	15-06-1999